# CENTER FOR DRUG EVALUATION AND RESEARCH

**Approval Package for:**

**Application Number : 040099**

**Trade Name : LORTAB 5/325**

**Generic Name: Hydrocodone Bitartrate and Acetaminophen Tablets USP 5mg/325mg**

**Sponsor : UCB Pharma, Inc.**

**Approval Date: June 25, 1997**

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION 040099**

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| | Included | Pending Completion | Not Prepared | Not Required |
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# CENTER FOR DRUG EVALUATION AND RESEARCH

**Application Number 040099**

## APPROVAL LETTER

ANDA 40-099

JUN 25 1997

UCB Pharma, Inc.
Attention: Patricia A. Fritz
1950 Lake Park Drive
Smyrna, GA 30080

Dear Madam:

This is in reference to your abbreviated new drug application dated March 14, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for LORTAB® 5/325 (Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/325 mg).

Reference is also made to your amendment dated January 31, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The drug product, Hydrocodone Bitartrate and Acetaminophen Tablets USP, 5 mg/325 mg (LORTAB® 5/325) can be expected to have the same therapeutic effect as that of the listed drug product upon which the Agency relied as the basis of safety and effectiveness. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ 6/24/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER 040099

## FINAL PRINTED LABELING

ucb Pharma

**PHARMACIST:** Dispense in a tight, light-resistant container with a child-resistant closure.
Store at controlled room temperature, 15°-30°C (59°-86°F).

NDC 50474-935-01 100 TABLETS

**Lortab® 5/325**

**USUAL DOSAGE:** See package insert for complete dosage recommendations.

APPROVED

JUN 25 1997

**HYDROCODONE* BITARTRATE AND ACETAMINOPHEN TABLETS, USP**
**5 mg/325 mg**

Lot No.:
Exp. Date:

*Warning: May be habit forming.

Manufactured for
**UCB Pharma, Inc.**
Atlanta, GA 30080
**by Mikart, Inc.**
Atlanta, GA 30318

**CAUTION:** Federal law prohibits dispensing without prescription.

N 3 50474-935-01 9

Rev. 1/96
Code 667B10
P/N FDA Sub.2

ucb Pharma

**PHARMACIST:** Dispense in a tight, light-resistant container with a child-resistant closure.

Store at controlled room temperature, 15°-30°C (59°-86°F).

NDC 50474-935-50 500 TABLETS

**Lortab® 5/325**

**USUAL DOSAGE:** See package insert for complete dosage recommendations.

APPROVED

JUN 25 1997

**HYDROCODONE* BITARTRATE AND ACETAMINOPHEN TABLETS, USP**
**5 mg/325 mg**

Lot No.:
Exp. Date:

*Warning: May be habit forming.

Manufactured for
**UCB Pharma, Inc.**
Atlanta, GA 30080
**by Mikart, Inc.**
Atlanta, GA 30318

**CAUTION:** Federal law prohibits dispensing without prescription.

N 3 50474-935-50 7

Rev. 5/95
P/N FDA Sub.2

Code 667B50

Acetaminophen: In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams, or fatalities with less than 15 grams.

**Treatment:** A single or multiple overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1 g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids. Vasopressors and other supportive measures should be employed as indicated. A cuffed endo-tracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypoprothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone hydrochloride 0.4 mg to 2 mg is given parenterally. Since the duration of action of hydrocodone may exceed that of the naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 g.

## DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to severity of pain and response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The usual adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage should not exceed 8 tablets.

## HOW SUPPLIED

Lortab 5/325 tablets (Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 5 mg/325 mg) contain hydrocodone bitartrate 5 mg (Warning: May be habit forming) and acetaminophen 325 mg. They are supplied as white with orange specks capsule-shaped, bisected tablets, debossed "Whitby/935," in containers of 100 tablets, NDC 50474-935-01, and in containers of 500 tablets, NDC 50474-935-50.

**Storage:** Store at controlled room temperature, 15°-30°C (59°-86°F).

Dispense in a tight, light-resistant container with a child-resistant closure.

**CAUTION:** Federal law prohibits dispensing without prescription.

A Schedule CIII Narcotic.

Manufactured For:
**UCB PHARMA, INC.**
Atlanta, GA 30080

Manufactured By:
**MIKART, INC.**
Atlanta, GA 30318

Rev. 1/96
Code 667B00
P/N FDA Sub.2

# LORTAB® 5/325

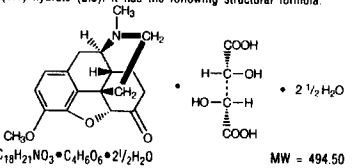
## HYDROCODONE* BITARTRATE AND ACETAMINOPHEN TABLETS, USP 5 mg/325 mg

***Warning: May be habit forming.**

## DESCRIPTION

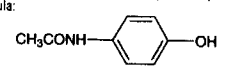
Hydrocodone bitartrate and acetaminophen is supplied in tablet form for oral administration.

Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:



$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2^1/_2H_2O$ MW = 494.50

Acetaminophen, 4'-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:



$C_8H_9NO_2$ MW = 151.16

Each Lortab 5/325 tablet contains:

| | |
|---|---|
| Hydrocodone Bitartrate | 5 mg |
| Warning: May be habit forming | |
| Acetaminophen | 325 mg |

In addition each tablet contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, crospovidone, microcrystalline cellulose, povidone, pregelatinized starch, stearic acid and sugar spheres which are composed of starch derived from corn, sucrose, and FD&C Yellow #6.

## CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating centers. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

**Pharmacokinetics:** The behavior of the individual components is described below.

Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6-α- and 6-β-hydroxymetabolites.

See OVERDOSAGE for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See OVERDOSAGE for toxicity information.

## INDICATIONS AND USAGE

Lortab 5/325 (Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 5 mg/325 mg) are indicated for the relief of moderate to moderately severe pain.

## CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone or acetaminophen.

## WARNINGS

**Respiratory Depression:** At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

**Head Injury and Increased Intracranial Pressure:** The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

**Acute Abdominal Conditions:** The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

## PRECAUTIONS

**General:** Special Risk Patients: As with any narcotic analgesic agent, Lortab 5/325 tablets should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when Lortab 5/325 tablets are used postoperatively and in patients with pulmonary disease.

**Information for Patients:** Hydrocodone, like all narcotics, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Hydrocodone may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

**Laboratory Tests:** In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

**Drug Interactions:** Patients receiving narcotics, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with hydrocodone bitartrate and acetaminophen tablets may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

**Drug/Laboratory Test Interactions:** Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** No adequate studies have been conducted in animals to determine whether hydrocodone or acetaminophen have a potential for carcinogenesis, mutagenesis, or impairment of fertility.

**Pregnancy:**

*Teratogenic Effects:* Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Lortab 5/325 tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

*Nonteratogenic Effects:* Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

**Labor and Delivery:** As with all narcotics, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

**Nursing Mothers:** Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from hydrocodone and acetaminophen, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.

## ADVERSE REACTIONS

The most frequently reported adverse reactions are light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in non-ambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:

**Central Nervous System:** Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.

**Gastrointestinal System:** Prolonged administration of Lortab 5/325 tablets may produce constipation.

**Genitourinary System:** Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.

**Respiratory Depression:** Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on brain stem respiratory centers (see OVERDOSAGE).

**Dermatological:** Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

Potential effects of high dosage are listed in the OVERDOSAGE section.

## DRUG ABUSE AND DEPENDENCE

**Controlled Substance:** Lortab 5/325 tablets (Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 5 mg/325 mg) are classified as a Schedule III controlled substance.

**Abuse and Dependence:** Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, this product should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when hydrocodone bitartrate and acetaminophen tablets are used for a short time for the treatment of pain.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The rate of development of tolerance varies among patients.

## OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen.

**Signs and Symptoms:**

Hydrocodone: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis) extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER 040099

## CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO #3

2. ANDA 40-099 (5mg/325 mg)

3. NAME AND ADDRESS OF APPLICANT
UCB Pharma, Inc.
Attention: Patricia A. Fritz
1950 Lake Park Drive
Smyrna, Georgia 30080

4. LEGAL BASIS FOR SUBMISSION
Vicodin Tablets- Knoll Pharmaceuticals
Expired and no patent information; no exclusivity
This ANDA was submitted based on an approved ANDA suitability petition under 314.93. The petition filed under section 505 (J)(2)(c) of the act where the Agency determined that the referenced product was suitable for submission as an ANDA.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
Lortab 5 mg/325 mg

7. NONPROPRIETARY NAME
Hydrocodone Bitartrate and Acetaminophen Tablets, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
March 14, 1994: Original submission.
April 21, 1994: Amendment.
April 22, 1994: Date acceptable for filing.
October 21, 1994: Amendment.
January 31, 1996

FDA:
April 7, 1994: Refuse to file letter.
May 19, 1994: Acknowledgement letter.
August 17, 1994: Deficiency letter.
April 3, 1995: Deficiency letter

10. PHARMACOLOGICAL CATEGORY
Narcotic analgesic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

(b)4 - Confidential Business

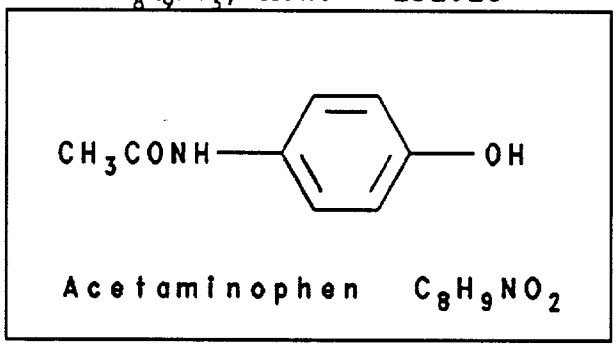
13. DOSAGE FORM
Tablets

14. POTENCY
5 mg/325 mg

15. CHEMICAL NAME AND STRUCTURE

Acetaminophen USP

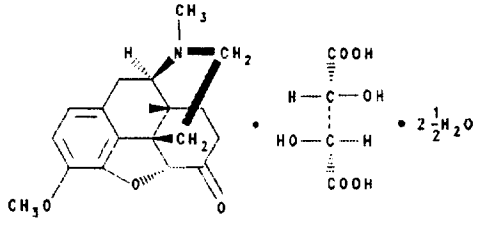
$C_8H_9NO_2$; M.W. = 151.16




4'-Hydroxyacetanilide. CAS [103-90-2]

Hydrocodone Bitartrate USP

$C_{18}H_{21}NO_3 . C_4H_6O_6 . 2½H_2O$




Hydrocodone Bitartrate $C_{18}H_{21}NO_3 . C_4H_6O_6 . 2\frac{1}{2}H_2O$

4,5α-Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). CAS [34195-34-1; 6190-38-1]

16. RECORDS AND REPORTS
N/A

17. COMMENTS
The following deficiencies are found:
- EER to be issued

18. CONCLUSIONS AND RECOMMENDATIONS
The application can be approved. Approval is pending for acceptable EER. The other Mikart applications were approved (ANDA# 81223, 89689, 89697, 89698 and 89699) for the same products in 1987 and 1989.

19. REVIEWER: Sema Basaran, Ph.D.

DATE COMPLETED:
6-13-96
6-25-96 (Labeling)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040099

# BIOEQUIVALENCE REVIEW(S)

JUN 22 1994

Hydrocodone Bitartrate/
Acetaminophen
5 mg/325 mg Tablets
ANDA # 40-099
Reviewer: James Chaney
WP #40099DW.394

Whitby Pharmaceuticals, Inc.
Richmond, Virginia
Submission Date:
March 8, 1994

## Review of Dissolution Data and Waiver Request

The firm has submitted dissolution data in support of a request for a bioequivalence study waiver as provided for under 21 CFR 320.22(c) for its hydrocodone bitartrate/acetaminophen, 5 mg/325 mg tablets (Lortab$^R$ 5/325) manufactured by Mikart, Inc. The listed drug is Vicodin Tablets (hydrocodone bitartrate and acetaminophen tablets, 5 mg/500 mg) manufactured and distributed by Knoll Pharmaceuticals, Inc.

Comments:

1. The dissolution method used was correct and satisfactory content uniformity data was submitted for the lot used in the dissolution testing.

2. The dissolution testing data demonstrate that the test and reference products meet the dissolution specifications (Table 1). The specifications state that not less than (b)4 of the labeled amount of hydrocodone bitartrate and not less than (b)4 of the labelled amount of acetaminophen is dissolved in 30 minutes. For both the test and reference products greater than (b)4 of the acetaminophen and greater than (b)4 of the hydrocodone bitartrate are dissolved.

3. This ANDA was submitted based on an approved ANDA suitability petition under 314.93. The petition was filed under Section 505 (j)(2)(c) of the Act where the Agency determined that the referenced product was suitable for submission as an ANDA. The petition was approved on June 8, 1987, under Docket Number 87 P-0129/CP. The reason for the petion was a new strength. A copy of the FDA letter to the firm approving the petition is included as Attachment I.

4. The reference product, Vicodin Tablets (hydrocodone bitartrate and acetaminophen tablets, 5 mg/500 mg), is classified AA in "Approved Drug Products with Therapeutic Equivalence Evaluations". The test product which differs only in formulation and a smaller amount of acetaminophen would also qualify for an AA rating. Therefore, since the dissolution testing is acceptable there would be no need to conduct an in vivo bioequivalence study.

5. The formulation of the test product is given in Table 2.

6. The firm did not include %CV's in its dissolution report. The %CV's were calculated by the reviewer. In any future submissions of dissolution data the firm should report these values.

Recommendations:

1. The in vitro dissolution testing conducted by Whitby Pharmaceuticals, Inc. on its hydrocodone bitartrate and acetaminophen 5 mg/325 mg tablets is acceptable.

2. The Division of Bioequivalence agrees that the information submitted by Whitby Pharmaceuticals, Inc. demonstrates that hydrocodone bitartrate and acetaminophen, 5 mg/325 mg tablets fall under 21 CFR 320.22 (c) of the Bioavailability/ Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the test product is granted.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of pH 5.8 phosphate buffer at 37° using USP XXII apparatus II (paddle) at 50 rpm. The test should meet the following specifications:

   Not less than (b)4 of the labeled amount of hydrocodone bitartrate and not less than (b)4 of the labelled amount of acetaminophen is dissolved in 30 minutes.

[redacted] med of the recommendations and comment 6.

/S/

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED ATWu
FT INITIALED ATWu [redacted] /S/ Date: 8/22/94

cc: Anda 40-099 original, HFD-630, HFD-600 (OGD), HFD-604 (Hare), HFC-130 (Allen), HFD-652 (Wu, Chaney), Drug File

JEC/062194/ntp/WP #40099DW.394

## Table 1. In Vitro Dissolution Testing

Drug (Generic Name):
Dose Strength: 5 mg/325 mg
ANDA No.: ANDA # 40-099
Firm: Whitby Pharmaceuticals, Inc.
Submission Date: March, 8, 1994
File Name: 40099DW.394

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: pH 5.8 Phosphate Buffer Volume: 900 ml
Specifications: NLT (b)4 of the hydrocodone bitartrate in 30 min,
NLT (b)4 of the acetaminophen in 30 min.
Reference Drug: Vicodin Tablets
Assay Methodology: (b)4 -

II. Results of In Vitro Dissolution Testing:

Acetaminophen

| Sampling Times (Minutes) | Test Product Lot # J93716 Strength(mg) 325 | | | Reference Product Lot # 10760363 Strength(mg) 500 | | |
|---|---|---|---|---|---|---|
| | Mean % | Range | %CV | Mean % | Range | %CV |
| 15 | 97.8 | (b)4 - Confidential Business | 0.75 | 82.8 | (b)4 - Confidential Business | 6.96 |
| 30 | 96.7 | | 3.57 | 86.9 | | 5.22 |
| 45 | 97.3 | | 1.38 | 89.3 | | 4.59 |
| 60 | 95.5 | | 5.27 | 90.8 | | 4.12 |

Hydrocodone Bitartrate

| Sampling Times (Minutes) | Test Product Lot # J93716 Strength(mg) 5 | | | Reference Product Lot # 10760363 Strength(mg) 5 | | |
|---|---|---|---|---|---|---|
| | Mean % | Range | %CV | Mean % | Range | %CV |
| 15 | 97.5 | (b)4 - Confidential Business | 2.96 | 96.9 | (b)4 - Confidential Business | 5.88 |
| 30 | 96.0 | | 4.52 | 100.1 | | 2.80 |
| 45 | 97.2 | | 2.95 | 99.6 | | 2.14 |
| 60 | 97.9 | | 3.10 | 100.6 | | 1.29 |

Table 2.

Formulation of Whitby Pharmaceuticals' Proposed Hydrocodone Bitartrate/Acetaminophen, 5 mg/325 mg Tablets (Lortab® 5/325)

Formulation

| Component | mg/Tablet |
|---|---|
| **Active Ingredients** | |
| Hydrocodone Bitartrate, USP | 5.0 |
| (b)4 - Confidential Business (Equivalent to 325.0 mg of Acetaminophen USP)* | (b)4 - |
| **Inactive Ingredients** | |
| Microcrystalline Cellulose, NF | (b)4 - Confidential Business |
| Croscarmellose Sodium NF | |
| Colloidal Silicon Dioxide, NF | |
| Sugar Spheres (b)4 - | |
| Srearic Acid NF (Powder) | |
| Total Tablet Weight | 520.0 |

* Excipients (b)4 - Confidential Business